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Ambient Water Quality Criteria: Beryllium

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BERYLLIUM

Ambient Water Quality Criteria

Criteria and Standards Division
Office of Water Planning and Standards
U.S. Environmental Protection Agency
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CRITERION DOCUMENT

BERYLLIUM

CRITERIA

Aquatic Life

For beryllium the criterion to protect freshwater aquatic life as derived using the Guidelines is "$e^{(1.24\ \ln(\text{hardness})-6.65)}$" as the 24-hour average concentration (see the figure "24-hour average beryllium concentration vs. hardness") and the concentration should not exceed "$e^{(1.24\ \ln(\text{hardness})-1.46)}$"(see the figure "maximum beryllium concentration vs. hardness") at any time.

For saltwater aquatic life, no criterion for beryllium can be derived using the Guidelines, and there are insufficient data to estimate a criterion using other procedures.

Human Health

For the maximum protection of human health from the potential carcinogenic effects of exposure to beryllium through ingestion of water and contaminated aquatic organisms, the ambient water concentration is zero. Concentrations of beryllium estimated to result in additional lifetime cancer risks ranging from no additional risk to an additional risk of 1 in 100,000 are presented in the Criterion Formulation section of this document. The Agency is considering setting criteria at an interm target risk level in the range of 10^{-5}, 10^{-6}, or 10^{-7} with corresponding criteria of 0.087 µg/l, 0.0087 µg/l, and 0.00087 µg/l, respectively.

BIBLIOGRAPHIC INFORMATION

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Section 304(a) of the Clean Water Act (33 U.S.C. 1314(a)), requires EPA to publish and periodically update water quality criteria. These criteria are to reflect the latest scientific knowledge on the identifiable effects of pollutants on public health and welfare, aquatic life, and recreation. This report presents water quality criteria for beryllium. It presents concentration criteria for the protection of fresh water and saltwater aquatic life. It presents 'safe' concentrations for humans, and in the case of suspect or proven carcinogens, gives various levels of incremental cancer risk. A section 304(a) water quality criterion is a qualitative or quantitative estimate of the concentration of a water constituent or pollutant in ambient waters which, when not exceeded, will ensure a water quality sufficient to protect a specified water use. Under the Act a criterion is a scientific entity, based solely on data and scientific judgment. It does not reflect considerations of economic or technological feasibility nor is it a water quality standard and in itself has, ...

KEYWORDS: *Water quality, *Toxicology, *Beryllium, *Water pollution effects(Humans), *Water pollution effects(Animals), *Toxic substances.

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Introduction

Beryllium is a dark gray metal of the alkaline earth family. It is less dense than aluminum and is used in the production of light alloys, copper and brass (Lange, 1956). World production was reported as approximately 250 tons annually, but much more reaches the environment as emissions from coal burning operations (Tepper, 1972a). Most common beryllium compounds are readily soluble in water. The hydroxide is soluble only to the extent of 2 mg/l (Lange, 1956). However, at this level beryllium is toxic to many aquatic species (Tarzwell and Henderson, 1960; Slonim, 1973; U.S. EPA, 1978). Beryllium forms chemical compounds in which its valence is +2. At acid pH it behaves as a cation but forms anionic complexes at pH greater than 8 (Knejci and Scheel, 1966). Kopp and Kroner (1967) identified beryllium in 5.4 percent of 1577 U.S. surface waters at concentrations ranging from 0.01 to 1.22 µg/l, with a mean of 0.19 µg/l. The major source of beryllium in the environment is the combustion of fossil fuels (Tepper, 1972a). Beryllium enters the waterways through weathering of rocks and soils, through atmospheric fallout and through discharges from industrial and municipal operations.

In the aquatic environment, beryllium is acutely toxic to fish at concentrations as low as 87 µg/l (Slonim, 1973) and chronically toxic to *Daphnia magna* at a concentration of less than 3 µg/l (U.S. EPA, 1978). Beryllium acute toxicity to fish is greatly affected by water quality. In very soft water, beryllium is reportedly more than 100 times as toxic

as in very hard water (Slonim and Slonim, 1973). Beryllium has been reported to bioconcentrate to levels 1,000 times those of the surrounding water (Goldberg, et al. 1971). Since beryllium is an element, it may be expected to persist indefinitely in the environment in some form.

Less than 50 percent of ingested beryllium was absorbed from the intestine of rats (Reeves, 1965). Inhaled insoluble beryllium compounds are cleared from the lungs only slowly, if at all (Van Cleave and Kaylor, 1955; Wagner, et al. 1969). Injected beryllium initially concentrates preferentially in liver and bone, but liver beryllium is gradually mobilized and transferred to the skeleton (Van Cleave and Kaylor, 1955). Beryllium has been shown to inhibit several enzyme systems, including alkaline phosphatase (Klemperer, et al. 1949; Grier, et al. 1949) phosphoglucomutase (Hashimoto, et al. 1967) and potassium activated ATPase (Toda, 1968).

Beryllium has been reported to interfere with DNA metabolism in liver (Marcotte and Witschi, 1972) and to induce chromosomal and mitotic abnormalities (Vegni Talluri and Guiggani, 1967). It has also been shown to increase misincorporation of nucleotides during polymerization by DNA polymerase (Luke, et al. 1975; Loeb and Sirover, 1977).

Intravenously administered beryllium has been found to be either excreted in urine or deposited in kidney or bone (Sutt, et al. 1950). Cows injected with beryllium excreted little of it in their milk (Mullen, et al. 1972). The half life for beryllium in several species ranged from 890 days in rats to 1,770 days in monkeys (Furchner, et al. 1973).

The LD50 for intravenously injected beryllium has been reported to be as low as 0.44 mg/kg in rats (Witschi and Aldridge, 1967). Ingested beryllium is much less toxic, with an oral LD50 of 9.7 mg/kg (U.S. EPA, 1977). Inhaled aersols were acutely toxic to rats at 194 $\mu g/m^3$ and caused pathologic changes within 3 months at 42 $\mu g/m$ (Vorwald, et al. 1966).

In humans short-term exposure to beryllium oxide in air at 4 mg/m^3 produced a high incidence of disease and some fatalities (Natl. Acad. Sci., 1958). Acute disease in humans has been produced by as little as 100 $\mu g/m^3$ (Hall, et al. 1959). NAS (1958) reported that human exposure to air containing 25 $\mu g/m^3$ or less did not produce acute disease.

In one form or another beryllium causes ocular inflammation and contact dermatitis, rhinitis, pharyngitis, tracheobronchitis and acute pneumonitis (Van Ordstrand, et al. 1945; Tepper, 1972a; Tepper, et al. 1961). In animals beryllium has caused rachitic bone changes (Guyatt, et al. 1933; Branion, et al. 1931) and osteosclerotic changes (Gardner and Heslington, 1946).

The onset of chronic toxicity in humans may follow exposure by as long as 5 years. Symptoms include pneumonitis with cough, chest pain, and general weakness (Hardy and Stoeckle, 1959). Systemic effects include right heart enlargement with cardiac failure, enlargement of liver and spleen, cyanosis, digital clubbing and kidney stones (Hall, et al. 1959).

Beryllium has been implicated as a teratogen in snails (Raven and Spronk, 1953) and has inhibited limb regeneration in the salamander, Amblystoma punctatum (Thorton, 1950).

Lung and bone cancers are firmly associated with beryllium exposure (Gardner and Heslington, 1946; Dutra, et al. 1951; Spencer, et al. 1968). While beryllium is known to cause these cancers when administered by inhalation or injection, it has not been shown to cause them by ingestion, although such studies have been conducted (Barnes, 1948; Schroeder and Mitchener, 1975a, b). While early human epidemiological studies were inconclusive, the bulk of more recent work supports the hypothesis that beryllium is a human carcinogen (Wagoner, et al. 1978; Berg and Burbank, 1972).

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AQUATIC LIFE TOXICOLOGY*

FRESHWATER ORGANISMS

Introduction

The available data base for the effects of beryllium on freshwater organisms is limited to seven species of fish, two species of salamanders, one invertebrate species, and one green alga. Chronic test data are not available for any species of fish. A chronic test conducted with the invertebrate, Daphnia magna, indicated significant effects at 7.3 ug/l. The data on a green alga indicate that it is a resistant species. Beryllium does not appear to bioconcentrate in fish to a great extent and has a short half-life in fish tissue.

Hardness and associated alkalinity has been shown to influence the toxicity of metals to freshwater organisms. The data indicate that the acute toxicity of beryllium to freshwater fish can be correlated with hardness with beryllium being more toxic in soft water.

*The reader is referred to the Guidelines for Deriving Water Quality Criteria for the Protection of Aquatic Life [43 FR 21506 (May 18, 1978) and 43 Fr 29028 (July 5, 1978)] and the Methodology Document in order to better understand the following discussion and recommendation. The following tables contain the appropriate data that were found in the literature, and at the bottom of each table are the calculations for deriving various measures of toxicity as described in the Guidelines.

Acute Toxicity

Tarzwell and Henderson (1960) exposed fathead minnows and bluegills to beryllium in static toxicity tests using both soft and hard dilution water (Table 1). They found that beryllium was more toxic in soft water than in hard water. The unadjusted 96-hour LC50 values for the fathead minnow ranged from 150 µg/l soft water to 20,000 µg/l in hard water. For the bluegill the 96-hour LC50 values were 1,300 µg/l in soft water and 12,000 µg/l in hard water. The 96-hour LC50 values for the fathead minnow and bluegill tested in soft water represent an order of magnitude differences in the sensitivity of these two species.

Slonim and Slonim (1973) also reported on the effect of water hardness on the toxicity of beryllium to fish (Table 1). They exposed guppies in static tests to four dilution waters with different hardnesses and developed an exponential equation to describe the relationship of toxicity to hardness. Toxicity increased with decreasing hardness.

Cardwell, et al. (1976) reported 96-hour LC50 values of beryllium for three species of fish using flow-through procedures and measured concentrations (Table 1). In a dilution water with a hardness of about 140 mg/l as $CaCO_3$, the 96-hour LC50 values ranged from 3,250 µg/l for juvenile fathead minnows to 4,800 µg/l for juvenile goldfish. Three tests with flagfish fry gave 96-hour LC50 values that varied from 3,530 to 4,440 µg/l.

The fathead minnow was the only species tested using both static and flow-through conditions. However, the dilution

waters were not similar; thus it is not possible to evaluate the adjustment factor for beryllium for test methods.

Following the Guidelines, an exponential equation describing the relationship of toxicity to hardness for fathead minnows, guppies, and bluegills was fit by least squares regression of the natural logarithms of the toxicity values and hardness. The slopes of these equations ranged from 0.74 for bluegills to 1.64 for the guppy, with a geometric mean of 1.24.

As a measure of relative species sensitivity to beryllium, logarithmic intercepts were calculated for each species by fitting the mean slope (1.24) through the geometric mean toxicity value and hardness for each species. These intercepts varied from 1.48 for fathead minnows to 2.29 for goldfish, with a average intercept of 1.91 for five fish species. This variation in intercepts indicates a range of species sensitivity to beryllium of only two-fold when corrected for hardness effects. The adjusted mean intercept (0.55) is below that for any species tested. Thus, the Final Fish Acute Value is given by: $e^{(1.24 \ln(\text{hardness})+0.55)}$.

Acute toxicity data for one freshwater invertebrate species, Daphnia magna, are available (Table 2). The adjusted 48-hour LC50 values are 1,175 and 6,691 µg/l. Since these tests were conducted at slightly differing hardnesses, no relationship of toxicity and hardness could be determined. However, it seems logical to assume that a similar relationship exists between acute beryllium toxicity and hardness for invertebrate species as was demonstrated for fish. Using the mean slope (1.24) from fish acute values, the

calculated logarithmic intercept for Daphnia magna was 1.58, indicating that this invertebrate species is of the same order of sensitivity to beryllium as the fish species tested. After adjustment using the species sensitivity factor, the intercept is -1.46. Thus, the Final Invertebrate Acute Value is given by: $e^{(1.24 \ln(\text{hardness})-1.46)}$, which also becomes the Final Acute Value.

Chronic Toxicity

No chronic tests have been conducted with freshwater fish. However, the chronic effects of beryllium on Daphnia magna have been studied (Table 3). Adverse effects on survival were found in one test at the lowest test concentration (36 µg/l). In the only other chronic test available, effects on reproduction were observed at 7.3 µg/l and no effects were observed at 3.8 µg/l. The unadjusted 48-hour EC50 determined with the same species and water is 2,500 µg/l (Kimball, Manuscript).

Since no other chronic fish or invertebrate data are available to establish the realtionship of chronic toxicity values and hardness, the realtionship was estimated using the slope (1.24) from fish acute values. The calculated intercept for the only available Daphnia magna chronic value is -5.02. The adjusted mean intercept (-6.65) is used to determine the Final Invertebrate Chronic Value which also becomes the Final Chronic Value: $e^{(1.24 \ln(\text{hardness})-6.65)}$, since no chronic test data are available for fish.

Plant Effects

There was one study describing the effects of beryllium on freshwater plants (Karlander and Krauss, 1972). Growth of the green alga, Chlorella vannieli, was inhibited at a concentration of 100,000 µg/l, which is the Final Plant Value (Table 4).

Residues

Bioconcentration of beryllium by the bluegill exposed for 28 days (U.S. EPA, 1978) gave a bioconcentration factor of 19 (Table 4) with a half-life of one day in the whole body. No maximum permissible tissue concentration is available; therefore, a Residue Limited Toxicant Concentration cannot be calculated.

Miscellaneous

Cardwell, et al. (1976) extended the exposure time past 96 hours for the acute tests with fathead minnows and goldfish (Table 6). For both species there was continued mortality after 96 hours of exposure in the flow-through test. For the fathead minnow, the LC50 values of 3,250 µg/l at 96 hours decreased to 2,200 µg/l at 336 hours. For the goldfish the LC50 value of 4,800 µg/l at 96 hours decreased to 3,300 µg/l at 240 hours. The 96-hour LC50 values for the brook trout and channel catfish were greater than 5,090 µg/l.

Slonim and Ray (1975) conducted acute tests using two species of salamanders. The two species were similar in sensitivity to the lethal effects of beryllium, and beryllium was more toxic in soft water. Sensitivity of the salamanders was similar to that for the guppy in hard water, but salamanders were less sensitive in soft water.

CRITERION FORMULATION

Freshwater - Aquatic Life

Summary of Available Data

All concentrations herein are expressed in terms of beryllium.

Final Fish Acute Value = $e^{(1.24\ \ln(\text{hardness})+0.55)}$

Final Invertebrate Acute Value = $e^{(1.24\ \ln(\text{hardness})-\ 1.46)}$

Final Acute Value = $e^{(1.24\ \ln(\text{hardness})-1.46)}$

Final Fish Chronic Value = not available

Final Invertebrate Chronic Value = $e^{(1.24\ \ln(\text{hardness})-\ 6.65)}$

Final Plant Value = 100,000 µg/l

Residue Limited Toxicant Concentration = not available

Final Chronic Value = $e^{(1.24\ \ln(\text{hardness})-6.65)}$

The maximum concentration of beryllium is the Final Acute Value of $e^{(1.24\ \ln(\text{hardness})-1.46)}$ and the 24-hour average concentration is the Final Chronic Value of $e^{(1.24\ \ln(\text{hardness})-6.65)}$. No important adverse effects on freshwater aquatic organisms have been reported to be caused by concentrations lower than the 24-hour average concentration.

CRITERION: For beryllium the criterion to protect freshwater aquatic life as derived using the Guidelines is "$e^{(1.24\ \ln(\text{hardness})-6.65)}$" as a 24-hour average (see figure 1 "24-hour average beryllium concentration vs. hardness") and the concentration should not exceed "$e^{(1.24\ \ln(\text{hardness})-1.46)}$" (see figure 2 "maximum beryllium concentration vs. hardness") at any time.

Figure 1: Beryllium Criterion
24-Hour Average Concentration

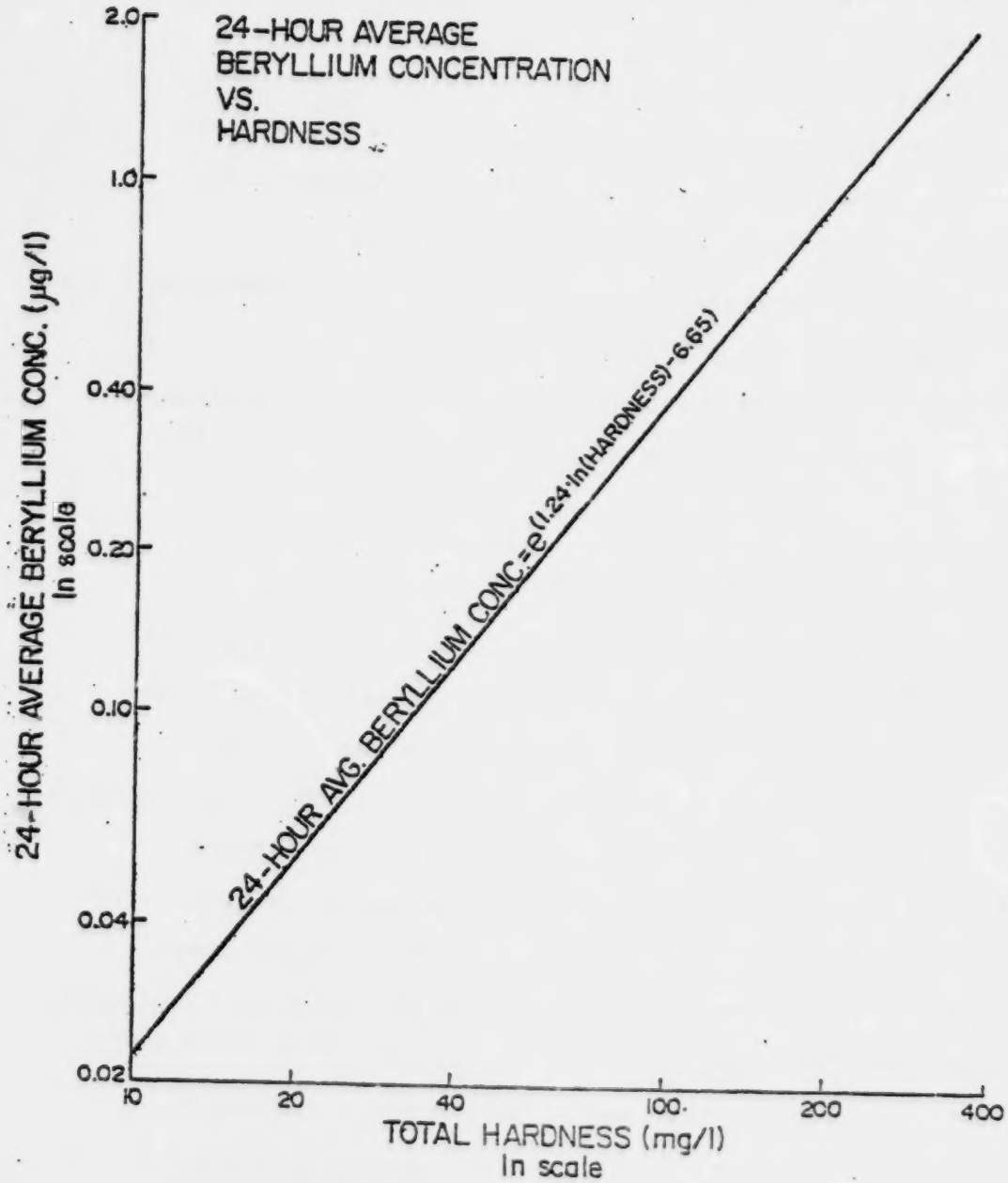

Figure 2: Beryllium Criterion
Maximum Concentration

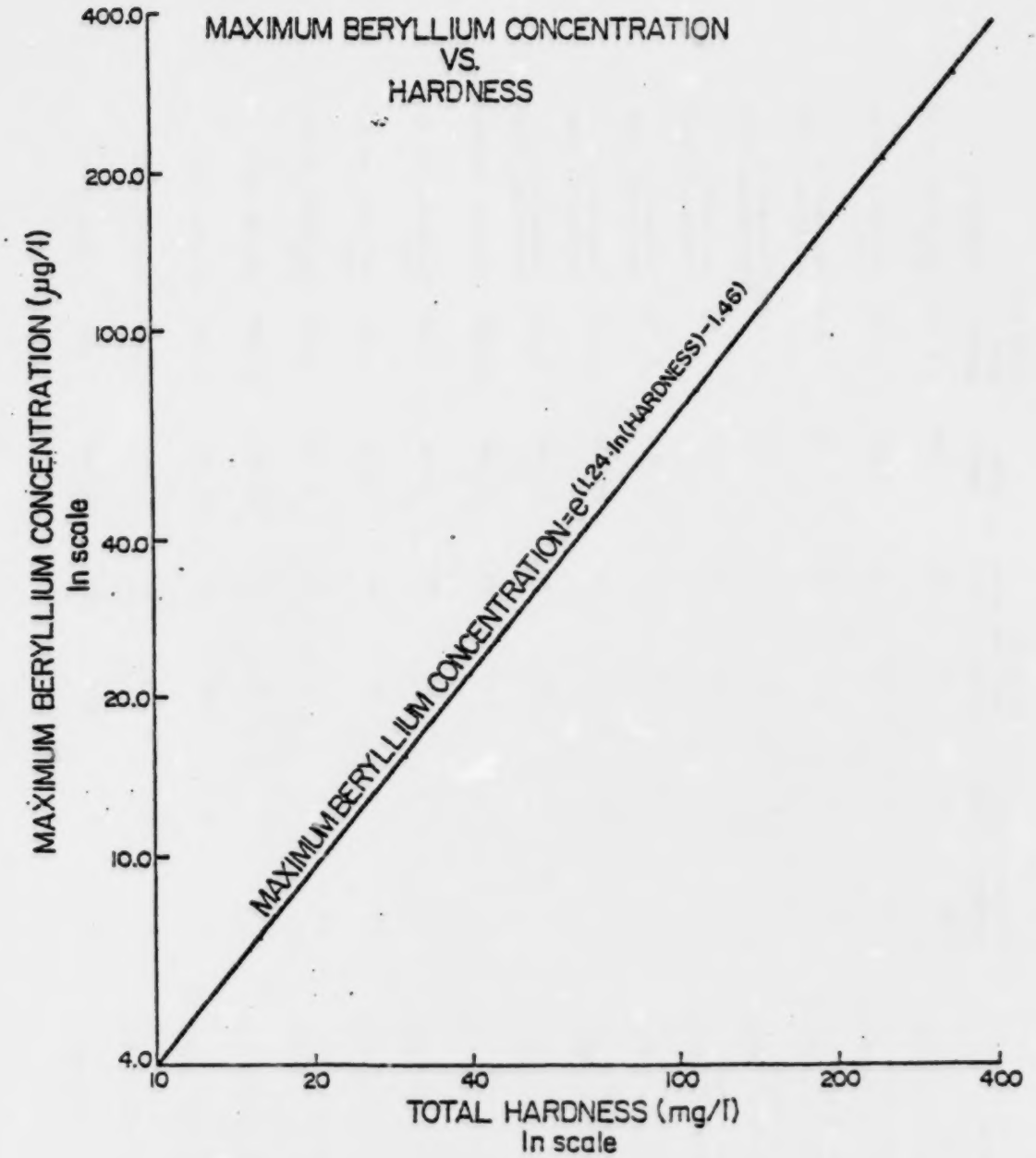

Table 1. Freshwater fish acute values for beryllium

Organism	Biomassay Method*	Test Conc.**	Hardness (mg/l as $CaCO_3$)	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Goldfish, Carassius auratus	FT	M	147	96	4,800	4,800	Cardwell, et al 1976
Fathead minnow, Pimephales promelas	FT	M	140	96	3,250	3,250	Cardwell, et al. 1976
Fathead minnow, Pimephales promelas	S	U	20	96	200	110	Tarzwell & Henderson, 1960
Fathead minnow, Pimephales promelas	S	U	20	96	150	82	Tarzwell & Henderson, 1960
Fathead minnow, Pimephales promelas	S	U	20	96	150	82	Tarzwell & Henderson, 1960
Fathead minnow, Pimephales promelas	S	U	400	96	11,000	6,000	Tarzwell & Henderson, 1960
Fathead minnow, Pimephales promelas	S	U	400	96	20,000	11,000	Tarzwell & Henderson, 1960
Fathead minnow, Pimephales promelas	S	U	400	96	15,000	8,200	Tarzwell & Henderson, 1960
Fathead minnow, Pimephales promelas	S	M	220	96	18,000	12,780	Kimball, Manuscript
Flagfish, Jordanella floridae	FT	M	140	96	4,440	4,440	Cardwell, et al. 1976
Flagfish, Jordanella floridae	FT	M	140	96	3,530	3,530	Cardwell, et al. 1976
Flagfish, Jordanella floridae	FT	M	140	96	3,530	3,530	Cardwell, et al. 1976
Guppy, Poecilia reticulata	S	U	450	96	32,000	17,500	Slonim, 1973
Guppy, Poecilia reticulata	S	U	450	96	28,000	15,300	Slonim, 1973
Guppy, Poecilia reticulata	S	U	450	96	32,000	17,500	Slonim, 1973
Guppy, Poecilia reticulata	S	U	450	96	24,000	13,100	Slonim, 1973

Table 1. (Continued)

Organism	Bioassay Method*	Test Conc.**	Hardness (mg/l as $CaCO_3$)	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Guppy, Poecilia reticulata	S	U	22	96	160	87	Slonim, 1973
Guppy, Poecilia reticulata	S	U	450	96	19,000	10,400	Slonim, 1973
Guppy, Poecilia reticulata	S	U	23	96	450	250	Slonim, 1973
Guppy, Poecilia reticulata	S	U	23	96	130	71	Slonim, 1973
Guppy, Poecilia reticulata	S	U	23	96	200	110	Slonim, 1973
Guppy, Poecilia reticulata	S	U	400	96	20,000	10,900	Slonim & Slonim, 1973
Guppy, Poecilia reticulata	S	U	275	96	13,700	7,500	Slonim & Slonim, 1973
Guppy, Poecilia reticulata	S	U	150	96	6,100	3,300	Slonim & Slonim, 1973
Guppy, Poecilia reticulata	S	U	22	96	160	87	Slonim & Slonim, 1973
Bluegill, Lepomis macrochirus	S	U	400	96	12,000	6,600	Tarzwell & Henderson, 1960
Bluegill, Lepomis macrochirus	S	U	20	96	1,300	710	Tarzwell & Henderson, 1960

* S = static, FT = flow-through

** U = unmeasured, M = measured

Adjusted LC50 vs. hardness:

Fathead minnow: slope = 1.58, intercept = -0.13, r = 0.97, p = 0.01, N = 8

Guppy: slope = 1.64, intercept = -0.41, r = 0.99, p = 0.01, N = 13

Bluegill: slope = 0.74, intercept = 4.34, r = 1.0, Not significant, N = 2

Table 1. (Continued)

Organism	Bioassay Method*	Test Conc.**	Hardness (mg/l as $CaCO_3$)	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference

Geometric mean slope = 1.24

Mean intercept for five fish species = 1.91

Adjusted mean intercept = 1.91-ln(3.9) = 0.55

Final Fish Acute Value = $e^{(1.24 \cdot \ln(\text{hardness})+0.55)}$

Table 2. Freshwater invertebrate acute values for beryllium

Organism	Bioassay Method*	Test Conc.**	Hardness (mg/l as $CaCO_3$)	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Cladoceran, Daphnia magna	S	U	180	48	7,900	6,691	U.S. EPA, 1978
Cladoceran, Daphnia magna	S	M	220	48	2,500	1,775	Kimball, Manuscript

* S = static

** U = unmeasured, M = measured

Adjusted LC50 vs. hardness:

No hardness relationship could be derived for any invertebrate species.

Using the geometric mean slope from the fish acute values, the intercept for D. magna = 1.58

Adjusted mean intercept = 1.58-ln(21) = -1.46

Final Invertebrate Acute Value = $e^{(1.24 \cdot \ln(\text{hardness})-1.46)}$

Table 3. Freshwater invertebrate chronic values for beryllium

Organism	Test*	Limits (ug/l)	Chronic Value (ug/l)	Hardness (mg/l as $CaCO_3$)	Reference
Cladoceran, Daphnia magna	LC	<36	<36	175	U.S. EPA, 1978
Cladoceran, Daphnia magna	LC	3.8-7.3	5.3	220	Kimball, Manuscript

* LC = life cycle or partial life cycle

Adjusted chronic values vs. hardness:

No hardness relationship could be derived for any invertebrate species.

Using the geometric mean slope from the fish acute values, the intercept for D. magna = -5.02

Adjusted mean intercept = $-5.02-\ln(5.1) = -6.65$

Final Invertebrate Chronic Value = $e^{(1.24 \cdot \ln(\text{hardness})-6.65)}$

Table 4. Freshwater plant effects for beryllium (Karlander & Krauss, 1972)

Organism	Effect	Concentration (ug/l)
Green alga, *Chlorella vannieli*	Growth inhibited at suboptimum conditions	100,000

Lowest plant value = 100,000 µg/l

Table 5. Freshwater residues for beryllium (U.S. EPA, 1978)

Organism	Bioconcentration Factor	Time (days)
Bluegill, *Lepomis macrochirus*	19	28

Table 6. Other freshwater data for beryllium

Organism	Test Duration	Effect	Hardness (mg/l as $CaCO_3$)	Result (ug/l)	Reference
Cladoceran, *Daphnia magna*	24 hrs	LC50	300	18,000	Bringman & Kühn, 1977
Cladoceran, *Daphnia magna*	21 days	Survival	175	<620	U.S. EPA, 1978
Brook trout, *Salvelinus fontinalis*	96 hrs	LC50	140	>5,090	Cardwell, et al. 1976
Goldfish, *Carassius auratus*	240 hrs	LC50	147	3,300	Cardwell, et al. 1976
Fathead minnow, *Pimephales promelas*	336 hrs	LC50	140	2,200	Cardwell, et al. 1976
Channel catfish, *Ictalurus punctatus*	96 hrs	LC50	140	>5,090	Cardwell, et al. 1976
Bluegill, *Lepomis macrochirus*	1 day	Half-life of residue = 1 day	180	--	U.S. EPA, 1978
Salamander, *Ambystoma maculatum*	96 hrs	LC50	22	3,150	Slonim & Ray, 1975
Salamander, *Ambystoma maculatum*	96 hrs	LC50	22	8,020	Slonim & Ray, 1975
Salamander, *Ambystoma maculatum*	96 hrs	LC50	22	8,320	Slonim & Ray, 1975
Salamander, *Ambystoma maculatum*	96 hrs	LC50	400	31,500	Slonim & Ray, 1975
Salamander, *Ambystoma maculatum*	96 hrs	LC50	400	18,200	Slonim & Ray, 1975
Salamander, *Ambystoma maculatum*	96 hrs	LC50	400	18,200	Slonim & Ray, 1975
Salamander, *Ambystoma opacum*	96 hrs	LC50	22	3,150	Slonim & Ray, 1975
Salamander, *Ambystoma opacum*	96 hrs	LC50	400	31,500	Slonim & Ray, 1975

SALTWATER ORGANISMS

Introduction

Jackim, et al. (1970) observed reduced alkaline phosphatase activity in the mummichog at concentrations of beryllium as low as 9 µg/l. Gross embryonic effects were observed in the sea urchin at a concentration of 9,010 µg/l (Evola-Maltese, 1959). No other data on the effects of beryllium on saltwater species are available.

Criterion Formulation

Saltwater - Aquatic Life

CRITERION: No saltwater criterion can be derived for beryllium using the Guidelines because no Final Chronic Value for either fish or invertebrate species or a good substitute for either value is available, and there are insufficient data to estimate a criterion using other procedures.

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Mammalian Toxicology and Human Health Effects

EXPOSURE

Ingestion

Kopp and Kroner (1967) reported the results of trace metal analyses of 1,577 drinking water samples obtained throughout the United States. Beryllium was detected in 5.4 percent of the samples. Concentrations ranged from 0.01 to 1.22 µg/l, with a mean value of 0.19 µg/l.

Petzow and Zorn (1974) found beryllium concentrations (dry weight) of 0.08 mg/kg in polished rice, 0.12 mg/kg in toasted bread, 0.17 mg/kg in potatoes, 0.24 mg/kg in tomatoes, and 0.33 mg/kg in head lettuce.

Meehan and Smythe (1967) determined beryllium levels in a variety of foodstuffs. Beryllium levels (ppm in ash) for different foodstuffs were: beans, 0.01; cabbage, 0.03; hen eggs, 0.01(yolk); milk, 0.02; mushrooms 0.12; nuts, 0.01-0.47; tomatoes, 0.02; and baker's yeast, .02.

A bioconcentration factor (BCF) relates the concentration of a chemical in water to the concentration in aquatic organisms. Since BCF's are not available for the edible portions of all four major groups of aquatic organisms consumed in the United States, some have to be estimated. A recent survey on fish and shellfish consumption in the United States (Cordle, et al. 1978) found that the per capita consumption is 18.7 g/day. From the data on the 19 major species identified in the survey, the relative consumption of the four major groups can be calculated.

A measured steady-state bioconcentration factor of 19 was obtained for beryllium using bluegills (U.S. EPA, 1978). Based on data for lead and cadmium, beryllium would probably have a lower BCF for fish and decapod muscle than for fish whole body, but probably would have a higher BCF for molluscs.

Group	Consumption (Percent)	Bioconcentration Factor
Freshwater fishes	12	5
Saltwater fishes	61	5
Saltwater molluscs	9	150
Saltwater decapods	18	5

Using the data for consumption and bioconcentration for each of these groups, the weighted average BCF for beryllium is 19 in consumed fish and shellfish.

Inhalation

The detection of beryllium in air is infrequent and usually in trace amounts. According to Tabor and Warren (1958) and the National Air Sampling Network (1968), beryllium was present in 12 percent of 440 samples analyzed from 16 cities. Concentrations ranged from 0.001 to 0.002 $\mu g/m^3$ in urban areas and considerably lower (0.00013 $\mu g/m^3$ in more rural areas. The U.S. EPA (1971) found that samples collected at 100 stations during 1964 to 1965 had a 24-hour average beryllium concentration of less than 0.0005 $\mu g/m^3$. The maximum beryllium value was 0.008 $\mu g/m^3$. At a beryllium extraction plant in Ohio, beryllium concentrations were generally around 2 $\mu g/m^3$ over a 7 year period (Breslin and

Harris, 1959).

The burning of coal for space heating and electric power generation appears to constitute the greatest threat to the environment. Tepper (1972A) calculated that if 500 million tons of Illinois and Appalachian coal with a beryllium content of 2.5 ppm were burned annually, the potential release of beryllium from coal in this country would approximate 1,260 tons or five times the world production. This could result in considerable contamination of soil, water and plants as well as air.

Dermal

Exposure to soluble beryllium compounds can cause contact dermatitis. It is not readily absorbed, however, since ionic beryllium becomes bound to epidermal constituents, mainly alkaline phosphatase and nucleic acids (Belman, 1969). In general, the incidence of beryllium dermatitis is primarily confined to occupational exposure.

PHARMACOKINETICS

Absorption

Studies by Hyslop, et al. (1943) showed the amount of beryllium retained by animals was small (0.006 percent) compared with that ingested. A reason for the limited absorption was due to precipitation of soluble salts in the alimentary tract while the insoluble compounds were not appreciably dissolved in serum or gastric juice. Low absorption was also described by Reeves (1965) who reported that 60 to 90 percent of the beryllium ingested by rats was recovered in the feces.

Distribution

Although the lungs are the primary point of entry for beryllium, they are not the principal site of deposition for soluble beryllium compounds. Citrated beryllium was almost completely mobilized from the lungs within 4 days following exposure (Van Cleave and Kaylor, 1955). Insoluble beryllium compounds such as beryllium ores, however, tend to remain in the lung indefinitely (Wagner, et al. 1969). Only 12 to 21 percent of high temperature fired BeO aerosols were cleared from the lungs of rats in 63 days (Sanders, et al. 1974). Increased levels of beryllium have been reported in the lymph nodes and lungs of humans more than 20 years after termination of occupational exposure (Sprince, et al. 1976).

Van Cleave and Kaylor (1955) studied the distribution of beryllium in rats. Following intravenous administration, beryllium was carried to all tissues and could be detected in most organs. During the first several weeks after injection, smaller doses (50 µg/Be/kg) tended to accumulate in the skeleton and larger doses (500 µg Be/kg) in the liver. After about 100 days beryllium was gradually mobilized from the liver of rats and transferred to the skeleton.

Studies with intravenous or intramuscularly injected ^{7}Be, a strong gamma emitter, indicated that both ionic and citrate complexed beryllium were definitely bone seekers (Crowley, et al. 1949; Klemperer, et al. 1952). Bone radiographs of the distal end of the femur revealed deposits of beryllium in osteoid tissue adjacent to the epiphyseal plate (Kaylor and Van Cleave, 1953). Studies with BeO, injected intratracheally in rats, indicated that the greatest

concentrations were deposited in the bone with the next most common sites being spleen, liver, kidney, and muscle (Spencer, et al. 1972).

Beryllium was shown to have a special affinity for nuclei and nucleoli in lung and liver cells (Witschi and Aldridge, 1968; Robinson, et al. 1968). According to Reeves (1977) the concensus of studies indicated that the bulk of circulating beryllium is in the form of a colloidal phosphate, probably absorbed on plasma α - globulin, with minor portions carried as citrate or hydroxide.

Metabolism

Early work concerning the metabolism of beryllium centered on its effects in producing rickets in animals. Several enzyme systems such as alkaline phosphatase (Klemperer, et al. 1949; Grier, et al. 1949), phosphoglucomutase (Hashimoto, et al. 1967) sodium and potassium activated ATPase (Toda, 1968) have been shown to be inhibited by micromolar beryllium concentrations. The rickets-producing effects of Be were thought to be due partly to the alkaline phosphatase inactivating action of beryllium, causing, in particular, an inhibition of endochondreal calcification of cartilage (Vorwald, et al. 1966). The physiological significance of the other enzyme effects has not yet been established.

Earlier studies suggesting that immunologic mechanisms are implicated in the toxicology of beryllium in chronic beryllium disease (Sterner and Eisenbud, 1951) are supported by more recent evidence. For example, Alekseeva (1965) produced hypersensitivity in guinea pigs by intradermal beryllium injections. Belman (1969) developed hypersensitivity

in guinea pigs by the application of beryllium fluoride to the skin. Vasil'eva (1969) induced skin hypersensitivity to beryllium chloride in rats.

In humans, Curtis (1951) showed that application of a cutaneous patch test containing non-irritating concentrations of soluble beryllium could elicit a positive reaction on subsequent testing of the same material. Resnick, et al. (1970) measured immunoglobin fractions and showed increased IgG in most patients who previously had acute beryllium reactions or a history of dermatitis.

Kharlamova and Potapova (1968) have shown that beryllium can be concentrated in the nuclei, while others (Marcotte and Witschi, 1972; Witschi, 1968, 1970) reported that beryllium interferes with DNA metabolism in the liver.

Beryllium has also been reported to induce chromosomal and mitotic abnormalities in cell cultures (Vegni-Talluri and Guiggiani, 1967). Exposure of calf thymus DNA to a 0.056N concentration of beryllium caused molecular aggregation and flocculation, pointing to an irreversible and deleterious effect of beryllium on nucleic acid (Needham, 1974). More recently, it has been shown that the beryllium ion (Be^{+2}) increases the misincorporation of nucleotides during polymerization by DNA polymerase (Luke, et al. 1975; Loeb and Sirover, 1977). A possible mechanism was considered to be associated with an inhibition of 3' - 5' exonuclease activity. This exonuclease which is an integral part of the polymerase is thought to perform an editing function to remove non-complementary (incorrect) nucleotides during polymerization (Brutlag and Kornberg,1972). Sirover and Loeb (1976) however,

using polymerase from avian myeloblastosis virus, showed that Be^{+2} altered the accuracy of DNA synthesis. This polymerase lacks 3' - 5' proof reading exonculease activity and thus may not excise a mismatched nucleotide. These results show that beryllium can influence the accuracy of DNA replication *in vitro* and suggest that it may have the same effect *in vivo*.

Excretion

Small doses of intravenously administered ^{7}Be in rats tended to be either excreted mostly in the urine or deposited in the kidney or bone (Scott, et al. 1950). Van Cleave and Kaylor (1955) reported that citrated beryllium sulfate given intratracheally was almost completely mobilized from the lungs after 4 days. Seventy-nine percent was eliminated, primarily in the urine, with the remainder deposited in the bones. At tracer levels, the non-citrated beryllium sulfate remained in the lungs somewhat longer but was also mobilized at a rapid rate after 16 days. Ultimately, the amounts deposited in the skeleton and excreted did not differ in comparison with the citrated form. Zorn, et al. (1977) reported that the concentration of beryllium from aerosol inhalation was high in the alveoli and nasopharyngeal region, but low in the terminal bronchioles. Evidently ciliary action clears the small airways quite rapidly. In general, a fraction of a dose of beryllium taken in either through the lung or digestive tract is excreted fairly quickly, with most of the remainder ultimately stored in the long bones. Once deposited it is removed very slowly. The half-life for ^{7}Be was reported to equal 1,210, 890, 1,770 and 1,270

days in mice, rats, monkeys and dogs, respectively (Furchner, et al. 1973).

Underwood (1951) showed that the mechanism of excretion was tubular. Attempts to rid the body of deposited beryllium with chelating agents have been successful in animal experiments (Schubert and White, 1950; Schubert and Rosenthal, 1959) but not in clinical experience (Dequinalt and Haguenoer, 1973). In studies conducted with cows an insignificant amount of injected radioactive beryllium was recovered in the milk (Mullen, et al. 1972).

EFFECTS

Acute and Subacute Toxicity

Intravenous beryllium is highly toxic to animals in small doses. The LD_{50} for 200 gram male rats injected intravenously with soluble beryllium salts was reported to be 0.44 mg Be/kg (Witschi and Aldridge, 1967), and 0.51 mg Be/kg for female rats injected with $BeSO_4$ (Vacher and Stoner, 1968). Death was attributed to biochemical disturbances caused by progressive destruction of liver tissue (Aldridge, et al. 1949). The effectiveness of beryllium was greatly decreased when ingested. The oral LD_{50} of $BeCl_2$ in rats was reported to be 9.7 mg/kg as Be (U.S. EPA, 1977). Rats survived for several weeks when fed diets containing up to 2 percent beryllium carbonate (Guyatt, et al. 1933) and at least 50 days when fed 0.24 gm/day beryllium carbonate (0.03 gm/day Be) (Businco, 1940). There have been no reported cases of oral toxicity in humans.

Inhaled BeO aerosol at a concentration of 194 $\mu g/m^3$ Be was acutely toxic to rats while 42 $\mu g/m^3$ produced pathologic changes within 3 months (Vorwald, et al. 1966). Concentrations acutely toxic in humans are less well defined. For example, concentrations of 30 mg/m^3 beryllium oxide in the air produced no acute cases in one short-term exposure of humans, while 4 mg/m^3 produced a high incidence of acute disease with fatalities in another (Natl. Acad. Sci. 1958). The differences were probably due to the temperature at which beryllium oxide was produced. If calcined at 500°C a relatively soluble product with large surface area is formed while calcining at 1,600°C results in an insoluble form. Beryllium oxide calcined at 500°C caused pulmonary damage in rabbits at dose levels of 2 mg/kg body weight when given intratracheally while beryllium oxide calcined at 1,600°C produced no reaction greater than expected for an inert dust (Spencer, et al. 1968).

The occurrence of acute disease following inhalation of highly soluble beryllium compounds was detected when concentrations exceeded 100 $\mu g/m^3$, with almost all personnel affected by concentrations greater than 1,000 $\mu g/m^3$ (Hall, et al. 1959). Unfortunately, the time periods for the above exposures were not specified. A report by the National Academy of Sciences (1958) indicated that acute beryllium disease did not occur in humans at ambient air concentrations of 25 $\mu g/m^3$ or less. In the same report no lung damage was reported in experimental animals exposed to 40 $\mu g/m^3$. Hardy (1955) reported that acute beryllium poisoning is related to the intensity of exposure with removal leading

to a disappearance of symptoms.

Tepper, et al. (1961) arbitrarily defined acute beryllium disease to include those beryllium induced disease patterns with less than 1 year natural duration. Diseases fitting this definition will be included in this category. The symptoms of acute toxicity have been described in detail by Tepper, et al. (1961), De Nardi, et al. (1953) and Hardy and Stoeckle (1959). Three general classes of effects include those affecting the skin, eye, and respiratory tract.

Acute skin effects include contact dermatitis characterized by reddened, elevated, or fluid-accumulated lesions on exposed surfaces (Van Ordstrand, et al. 1945). This disease has not been seen in workers handling insoluble forms of beryllium such as beryllium hydroxide, pure beryllium, and vacuum cast beryllium (Comm. Occ. Dis. Chest, 1965), but may occur following contact with soluble beryllium salts (McCord, 1951).

Beryllium ulcers result from implantation of soluble or insoluble beryllium materials in cutaneous areas previously injured as a result of abrasions, cuts, etc. Removal of the foreign material is necessary for healing to take place.

Ocular effects include inflammation of the conjunctiva from splash burns or in association with contact dermatitis (Van Ordstrand, et al. 1945). Corneal burns may occur resembling those produced by acids and alkalis.

Respiratory effects include rhinitis, pharyngitis, tracheobronchitis, and acute pneumonitis. The following response to a relatively soluble compound, beryllium oxide calcined at 500°C was described by Tepper (1972b) as a widely dispersed focal pneumonitis of granulomatous nature. The lesions had a dense central core of proliferating histiocytes clustered around aggregations of beryllium oxide particles often invested by epitheliod cells and one or two layers of fibroblasts. A few lymphocytes, plasma cells, or occasional multinucleated giant cells participated in the reaction. With time the lesions became less cellular, more collagenous, and finally hyalinized. The degree of effects can vary widely, with recovery times ranging from 1 to 6 weeks for mild cases and up to 6 months after acute pneumonia. Tepper, et al. (1961) reported 18 cases of acute beryllium pneumonitis fatalities following development of pulmonary edema.

Beryllium rhinitis and pharyngitis involve inflammation of the nasal mucosa and pharynx, frequently accompanied by mild nosebleeds. Fluid and blood accumulate in the mucous membranes and ulcerations occur. This condition is difficult to diagnose since it closely resembles that seen with the common cold.

Acute tracheobronchitis also results in non-specific symptoms. The effects are characterized by non-productive spasmodic cough, substernal discomfort, burning, tightness of the chest, and moderate difficulty with breathing upon exertion. Recovery is usually complete within 1 to 4 weeks (De Nardi, et al. 1953).

Most of the acute respiratory symptoms and pathologic changes cannot be differentiated from the inflammatory rection to other types of irritants. Positive identification may require a knowledge of past exposure and possible tissue analysis. The onset of acute respiratory symptoms can occur within a few hours after brief exposure to a high concentration of beryllium. More commonly, however, the illness is insidious in nature, developing over 1 to 3 weeks (Tepper, et al. 1961).

Acute pneumonitis has been produced by inhalation of virtually all beryllium compounds. These include beryllium metal, oxide, sulfate, fluoride, hydroxide, and chloride (Durocher, 1969). The acute changes result from the inhalation and deposition of beryllium compounds either as mists of the soluble salts or as fumes and dust of the relatively insoluble compounds, primarily the oxides.

Chronic Toxicity

Chronic beryllium disease differs from the acute form in several ways: (1) its occurrence is often separated from the time of exposure by periods ranging up to several years; (2) it has a prolonged duration with little evidence of a lasting cure; (3) it is commonly progressive in spite of cessation of exposure; and (4) it is a systemic disease (Tepper, et al. 1961). A study of chronic beryllium cases by Hardy and Stoeckle (1959) showed the latent period between last exposure and the onset of symptoms to vary, with 41 percent of the symptoms being manifested in the first month and 29 percent in 1 to 5 years. The most common clinical symptoms include granulomatous inflammation of the lungs,

with accompanying cough, chest pain, and general weakness (Hardy and Stoeckle, 1959). Systemic effects include right heart enlargement with accompanying cardiac failure, enlargement of the liver and spleen, cyanosis, digital clubbing, and the appearance of kidney stones (Hall, et al. 1959). A systemic effect reported in dogs, rabbits, and rats, but not in man, is the development of a macrocytic anemia (Stokinger, et al. 1951).

One of the earliest observed effects of beryllium toxicity was the development of a rachitic bone change after addition of soluble beryllium salts to the diet of poultry and livestock (Branion, et al. 1931; Guyatt, et al. 1933; Kay and Guyatt, 1933; Kay and Skill, 1934). Osteosclerotic changes were also noted in rabbits when beryllium was given intravenously (Gardner and Heslington, 1946).

Beryllium rickets is a disease that has not been reported in man. While there is no reason to believe it cannot be induced in humans, the concentrations in the food or water required to produce rickets in animals (0.125 percent beryllium carbonate for a mild case (Guyatt, et al. 1933)) make this an unlikely occurrence.

The predominant pulmonary pathology consists of an interstitial diffuse inflammatory process which is distinctively chronic in nature and without the edemetous and exudative changes seen in acute disease. The scattered focal lesions are composed mainly of large monocytes and are irregular in shape due to extensions into contiguous alveolar walls which are variously thickened with inflammatory cells (Vorwald, 1966). Granulomatous lesions are also seen in skin, liver,

kidney, lymph nodes, and skeletal muscles (Dudley, 1959).

Chronic beryllium disease can be produced in experimental animals with low concentrations of soluble beryllium compounds. Rats exposed for up to 6 months to an aerosol of 35 $\mu g/m^3$ $BeSO_4$ developed typical chronic pneumonitis along with granulomatous lesions and some neoplasms (Schepers, et al. 1957). Exposure of monkeys to 35 $\mu g/m^3$ $BeSo_4$ or to intratracheal instillations of a 5 percent suspension of beryllium oxide resulted in chronic pneumonitis in all animals (Vorwald, et al. 1966). Exposure of rats for 560 days to aerosols containing 2.8 $\mu g/m^3$ beryllium did not result in significant effects while 21 $\mu g/m^3$ produced changes only in long surviving rats (Vorwald, et al. 1966).

Concentrations of beryllium resulting in chronic disease in humans are more difficult to determine. Chronic and acute beryllium poisoning were common prior to setting of air standards in 1949, but lack of consistent monitoring prior to this time makes it difficult to relate exposure levels to disease. Ambient air concentrations were evidently quite high. For example, a 1946 survey of a beryllium plant by Laskin, et al. (1946) indicated beryllium dust concentrations of 110 to 533 $\mu g/m^3$ during beryllium furnace coke removal operation. Zielinski (1961) reported levels of 11,330 to 43,300 $\mu g/m^3$ in a beryllium alloy plant.

Since the early 1950's evidence was presented indicating that the 2 $\mu g/m^3$ standard was generally being met. For example, at one beryllium extraction plant, ambient air concentrations measured over a 7 year period were at or

below 2 $\mu g/m^3$ (Breslin and Harris, 1959). Williams (1961) presented results of surveys of beryllium exposures in 15 plants of various types which indicated that exposures were effectively controlled below the current standard in the preponderance of cases. Nevertheless, 76 new cases of beryllium disease have been added to the beryllium case registry from 1966 to 1974 of which at least 36 involved exposure since 1949 (Hasan and Kazemi, 1974).

A more recent study indicated that beryllium pollution was not being effectively controlled at all production facilities. Kanarek, et al. (1973) reported that ambient air concentrations at a beryllium extraction and processing plant ranged up to 50 times that of the accepted peak concentration of 25 $\mu g/m^3$. Some of the concentrations are listed below:

Location	Operation	Range of beryllium concentration $\mu g/m^3$
A. Billet Plant	All	0.35-213
	Fluoride area	0.67-213
	Reduction	0.43-22.5
	Hydroxide	2.0-33.2
	Bead handling	1.8-88
B. Fabrication Plant	All	0.31-1310
	Vacuum drying	1.74-1310
	Vacuum furnace	3.67-15.31
	Die loading	7.0-24.4
	Power handling	7.85-219
	Material transfer	3.90-1290
	Machine shop	0.31-6.4

Two hundred fourteen of the 245 full-time employees at this plant were studied in 1971. Thirty-one had chest radiographic abnormalities compatible with interstitial disease and 20 had hypoxemia at rest. A follow-up was conducted during 1974 (Sprince, et al. 1978). New engineering and safety controls had resulted in a decrease in peak concentrations of beryllium to less than 25 $\mu g/m^3$ in all work areas. In the vacuum drying area the peak concentration had decreased from 1,310 $\mu g/m^3$ to less than 2 $\mu g/m^3$. Improvement was noted in 13 of 20 workers previously indentified as hypoxemic. Eighteen of 31 with radiographic abnormalities in 1971 were available for follow-up. Of these 9 had reverted to normal.

Not all cases of chronic beryllium disease occurred during industrial exposure. Sterner and Eisenbud (1951) reported 13 cases within 3/4 of a mile from one beryllium plant. Air concentrations of beryllium were reported to range from 0.01 to 0.1 $\mu g/m^3$. By 1960 the beryllium case registry contained 47 well-documented cases of so-called neighborhood disease (Tepper, et al. 1961). If these cases were due to concentrations as low as those found in the ambient air an immune response would be required. However, Lieben and Williams (1969) reported that all the non-occupational cases studied by them could be attributed to contact with beryllium through routes other than outdoor air pollution. This included handling of polluted garments or other contact with contaminated objects or people. It is thus uncertain whether concentrations of 0.01 to 0.1 $\mu g/m^3$ beryllium in the air can cause beryllium disease.

Synergism and Antagonism

Studies conducted in attempting to discover a therapeutic agent that would neutralize the acute biologic effect of toxic beryllium compounds were summarized by Vorwald, et al. (1966). The only compound discovered up to this time having a reasonable degree of effectiveness in laboratory animals was aurintricarboxylic acid (ATA). This compound formed a chelate that tended to accumulate in the kidneys and spleen but not in the bones. The use of salicylates in conjunction with ATA was also considered beneficial. ATA was mildly toxic with an intravenous LD_{50} of 440 mg/kg for mice and 450 mg/kg for rats. The use of chelating agents for the alleviation of chronic poisoning, however, was not effective in clinical trials (Reeves, 1977).

Beryllium oxide was reported to potentiate the carcinogenicity of 20-methyl cholanthrene (20-MC) to a much higher degree than did carbon black (Uzawa, 1963). The fluoride ion has a synergistic effect on the acute toxicity of beryllium. Inhaled BeF_2 produced about twice the toxic effect in laboratory animals as $BeSO_4$ at any given concentration (Stokinger, et al. 1950).

Teratogenicity

Information relating to possible teratogenic effects of beryllium is limited. Beryllium was reported to inhibit the embryonic development of the snail, Lymnea stagnalis, with resulting peculiar morphogenic abnormalities (Raven and Spronk, 1953). Thornton (1950) observed inhibition of regeneration of the limbs of the salamander, Amblystoma punctatum, when immersed in 0.05 molar beryllium nitrate

solution. A pregnant rat fed 75 mg beryllium carbonate daily delivered three offspring of normal weight and appearance. Treatment, however, was not begun until the 18th day of pregnancy, well past the critical period for teratogenic effects (Businco, 1940).

Carcinogenicity

Lung cancer and bone cancer, or osteosarcoma, are the two types of malignancies commonly induced in experimental animals by beryllium. Osteosarcoma was first reported by Gardner and Heslington (1946). Their results have since been confirmed numerous times. These studies are listed in Table 1. As can be seen in the table, the great majority of the studies were carried out using rabbits injected intravenously. Dutra, et al. (1951) reported the only case of osteosarcoma from inhalation of a beryllium compound. Most compounds tested appeared to be effective in producing osteosarcoma when injected intravenously, even metallic beryllium.

Studies designed to induce lung cancer are listed in Table 2. As can be seen, inhalation or intratracheal instillation of the beryllium compounds were the primary routes of administration. Occasionally, lung cancer did occur with intravenous injection but this was due to metastases from the bone. In general, the more soluble compounds are more effective in producing both lung cancer and berylliosis. For example, beryllium oxide produced at a temperature of 500^{o}C was much more effective than that produced at 1,600^{o}C, with the primary difference being solubility (Spencer, et al. 1968).

Despite the large number of studies implicating beryllium as a carcinogen, there are no recorded instances of cancer being produced by ingestion. As reviewed previously, large concentrations of beryllium carbonate were fed to animals in the 1930's to produce a type of osteosclerosis. Although osteosarcoma was not reported, the experiments were generally terminated before the development of cancer would be expected. Casarotto (1952) also failed to detect tumors in the parathyroid glands or teeth (the only organs studied) of two dogs, one fed 1.3 gm beryllium carbonate per day for 104 days and the other 0.5 to 1.5 gm per day for 109 days. In longer term studies, however, Barnes (1948) failed to detect tumors in mice administered 1 percent beryllium sulfate in the drinking water for 1 year.

More recently, beryllium sulfate at a concentration of 5 ppm as Be in the food, over a life time, caused no change in growth rates of mice or rats, longevity, or incidence of tumors (Schroeder and Mitchener, 1975a,b), except for a small excess rate of lymphoma leukemias in female mice and in grossly observed tumors of all sites in male rats.

The lack of a significant effect may be due to the small absorption of Be from the gastrointestinal tract. If Be is carcinogenic via ingestion it may be less potent than observed by Schroeder and Mitchener. In the male rats given 5 ppm in the drinking water, nine of 33 animals had grossly observed tumors of some type, whereas four of 26 controls had tumors.

Cancer Epidemiology

The majority of exposures to high levels of beryllium took place in the 1940's. Due to a lack of appreciation of the harmful effects, insufficient monitoring information, and a lack of a centralized data base prior to 1951; studies attempting to link beryllium to cancer in humans were not carried out until many years later. Stoeckle, et al. (1969) reported no incidence of cancer in 60 selected cases of beryllium disease first diagnosed between 1944 and 1966. Bayliss (1972) studied records from 3,921 males employed in two beryllium plants from January 1942 through December 1967. Mortality from respiratory tract cancer revealed no significant departure from expectation in this population. Hardy, et al. (1967) reported 14 cases of cancer among a group of 535 individuals listed in the Beryllium Case Registry in 1966. These included 3 cases of lung cancer, 3 of bone sarcoma, and one each of cancer of the cervix, skin, CNS, cecum, breast, eye, colon, and nasopharynx. According to Hardy (1976), the bone sarcomas were incorrectly listed and represented only one case. Overall, a significant increase in the incidence of bone or lung cancer could not be detected.

Mancuso (1970) reported 9 deaths due to lung cancer in a cohort of 594 beryllium workers above age 25 at one company, 6 of whom were among 142 individuals indentified as having had prior beryllium-related bronchitis and pneumonitis during 1937-1948. The age-adjusted lung cancer mortality rate was calculated to equal 284.3 per 100,000 polulation for the sub-cohort with prior respiratory illness, compared

with 77.7 per 100,000 for the main cohort. Workers who were employed 1-5 calendar quarters had a higher lung cancer rate than those employed for 6 quarters or more. It was concluded that prior respiratory illness of beryllium workers is associated with high lung cancer mortality rate, but the reverse length-of-exposure/rate-of-incidence correlation could not be explained. Hasan and Kazemi (1974) reported 4 cases of lung cancer among 76 cases added to the registry since 1966, making the total incidence of lung cancer in the U.S. Beryllium Case Registry, as of 1974, 7 in 611, or 1.14 percent.

Niemöller (1963) described 3 cases of lung carcinoma that he felt were related to beryllium exposure. Two were exposed to beryllium industrially and the third was a smoker. Niemoller based his conclusion on the location of tumors, a history of exposure (either industrial or through smoking), and the presence of beryllium in the tissue. Gold (1967) described a peritoneal mesothelioma of the recto-vaginal septum in a 34-year-old woman. The patient had a history of traumatic vaginal lesions repeatedly exposed by douching with hard water containing soluble beryllium at a level of 0.035 µg/l; the patient also had environmental exposure to asbestos. Analysis of tumor tissue showed presence of beryllium at a level of 0.04 µg/g; asbestos was not demonstrated. This author also believed that the tumor was beryllium-related but the identification of the etiologic factor in all these cases was somewhat conjectural.

Berg and Burbank (1972) observed significant positive correlation between beryllium concentration in drinking water and cancer deaths in 15 regions of the country, ranked according to levels of trace metals. The highest mean positive level was 0.3 μg Be/l for the states Delaware, Maryland, West Virginia, and Kentucky. Cancers of breast, bone, and uterus appeared to have a probability of positive association ranging from 0.006 to 0.040, but the association was weak in subgroups.

Three very recently completed and thus far unpublished studies have also claimed that beryllium exposure increased the risk of cancer mortality. These are an updating of the former Bayliss study (Wagoner, Infante, and Bayliss, 1978), an updating of the former Mancuso study (Mancuso, 1978), and a study by NIOSH based on the case reports in the U.S. Beryllium Registry (Infante, Wagoner, and Sprince, 1978). These papers, or their preliminary drafts, were entered in the record of the hearing on the proposed standard for exposure to beryllium (OSHA, 1977) and were the subject of considerable controversy (Shapley, 1977; Wagoner et al., 1978). The matter was reviewed by a panel of uninvolved

experts convened for this purpose by the Secretary of H.E.W., and resulted in the following statement:

> The epidemiologic evidence is suggestive that beryllium is a carcinogen in man. The evidence is not at this time judged to be more than suggestive because alternative explanations for the positive findings have not been definitely excluded...Specially designed case control studies are needed to evaluate other risk factors in the beryllium-associated lung cancer cases. Confirmatory retrospective cohort studies should also be conducted. Nevertheless, it would be imprudent from a public health perspective to delay our judgment about beryllium exposure of current workers until these studies are completed. In our opinion, beryllium should be considered as a suspect carcinogen for exposed workers. (Discher, 1978).

CRITERION FORMULATION

Existing Guidelines and Standards

The present standard for occupational exposure prescribes an 8-hour time weighted average of 2.0 $\mu g/m^3$ with a ceiling concentration of 5.0 $\mu g/m^3$. In addition, the present standard allows a peak concentration above the ceiling concentration of 25 $\mu g/m^3$ for a maximum duration of 30 minutes (Federal Register, 1975).

Beryllium is the subject of a Criterion Document (Occupational Safety and Health Administration, 1977). OSHA recommends that occupational exposure to beryllium and its compounds not exceed 1 $\mu g/m^3$ (averaged over an 8 hour work day) and a ceiling limit of 5 $\mu g/m^3$ (measured over a 15 minute sampling period).

The threshold limit value (TLV) for beryllium was set at 2 $\mu g/m^3$ by the American Conference of Governmental Industrial Hygienists (1977).

National Emission Standards for Hazardous Air Pollutants set their criterion as: not more than 10 grams in 24 hours or emissions which result in maximum outplant concentrations of 0.01 $\mu g/m^3$, 30-day average (U.S. EPA, 1977).

The U.S. Environmental Protection Agency proposed a water quality standard of 11 $\mu g/l$ for the protection of aquatic life in soft fresh water; 1,100 $\mu g/l$ for the protection of aquatic life in hard fresh water; 100 $\mu g/l$ for continuous irrigation on all soils except 500 mg/l for irrigation on neutral to alkaline lime-textured soils. (U.S. EPA, 1977).

The National Academy of Science/National Academy of Engineering (1973) Water Quality Criteria recommendation for marine aquatic life is: hazard level - 1.5 μg/l; minimal risk of deleterious effects - 0.1 mg/l; application factor -0.01 (applied to 96-hr LC_{50}). Their recommendation for irrigation water is: 0.10 mg/l for continuous use on all soils.

Current Levels of Exposure

Concentrations of beryllium in the water supplies tend to be quite low. For example, analysis of 1,577 samples from U.S. surface waters and lakes showed beryllium present in 5.4 percent of the samples with concentrations ranging from 0.01 to 1.22 μg/l with a mean of 0.19 μg/l (Kopp and Kroner, 1967). The concentration of beryllium in seawater was reported equal to $6X10^{-4}$ μg/l (Goldberg, 1965).

Measurements of beryllium in air samples collected from 100 stations of the National Air Sampling Network (U.S. EPA, 1971) indicated that the average 24-hour concentration was less than 0.0005 $\mu g/m^3$. The maximum value recorded at these stations during 1964 - 1965 was 0.0008 $\mu g/m^3$. Thus, the maximum reported value was only 0.4 percent of the threshold limit value set by the American Conference of Governmental Industrial Hygienists (1977). Sussman, et al. (1959) reported an average concentration of 0.0281 $\mu g/m^3$ within one-half mile of a large beryllium plant near Reading, PA. Concentrations closer to the plant reached 0.0827 $\mu g/m^3$. Three brands of West German cigarettes were reported to contain beryllium levels of 0.47, 0.68, and 0.74 μg per cigarette with 4.5, 1.6, and 10.0 percent of the beryllium content, respectively, inhaled in the smoke

(Petzow and Zorn, 1974). These investigators estimated that the total beryllium intake for humans was about 100 ug/day with only a minor fraction by inhalation. Analysis of lung tissue at autopsy, from persons with no known industrial exposure to beryllium, showed maximum concentrations of 1.98 ug/100 gm tissue (Cholak, 1959).

Special Groups at Risk

Studies such as those of Sterner and Eisenbud (1951) have suggested that a small percentage of the population is sensitive to extremely low concentrations of beryllium in the air, probably through the development of an immune reaction. There is no evidence at present for the development of sensitivity to concentrations of beryllium present in food or water or that sensitivity to low levels of beryllium in the air is aggravated by ingestion of beryllium. No other special groups can be identified as special risks.

Basis and Derivation for the Criterion

Experiments have shown cancer by beryllium can be experimentally produced in laboratory animals. As can be seen in Tables 1 and 2, cancer has been produced by inhalation, intratracheal instillation, and intravenous injection of beryllium. Beryllium chloride has been shown to increase the error frequency of nucleotide base incorporation into DNA in an *in vitro* assay designed to detect potential metal mutagen/carcinogens (Sirover and Loeb, 1976). Finally, evidence is accumulating that inhalation of beryllium may cause lung cancer in humans.

Epidemiological studies have failed to establish an incontrovertible link between beryllium exposure and human cancer, and cancer was not produced in one experimental

study by ingestion of beryllium. However, beryllium has definitely been shown to induce osteosarcomas in rabbits following intravenous administration (Cloudman, 1949). Therefore, it is possible that cancer would be induced in humans if a large enough amount of beryllium were ingested. The occurrence of beryllium rickets after ingestion of food supplemented with beryllium sulfate shows that toxic amounts can be absorbed. In addition, Reeves (1965) reported data that show that 0.35 percent of ingested beryllium is retained in the tissue of rats after 24 weeks of feeding.

The only experiments conducted to date in which beryllium was ingested over a long period of time were those of Schroeder and Mitchener (1975a,b). Five ppm beryllium was added to the food and water of rats for a lifetime. Although Schroeder and Mitchener found no statistically significant difference in tumor frequency between controls and experimental rats and mice, there was a slight excess of lymphoma leukemias in the treated group compared to the controls.

The high frequency of osteosarcomas induced in rabbits given Be intravenously, the results of mutagenicity studies, and the ingestion-uptake-retention studies of Be, comprise a strong argument that Be-laden water poses a carcinogenic risk.

Although the Schroeder and Mitchener "lymphoma leukemia" experiment showed an effect significant at the .09 level, this result is sufficient to calculate a criterion level as long as it is remembered: 1) that it is not the Schroeder and Mitchener, but the previously mentioned results that establish that Be poses a carcinogenic risk to man, and

that, 2) we are relying on the Schroeder and Mitchener study because it is the only available data for oral ingestion from which a concentration range can be calculated. To extrapolate from the Be studies where the route of administration was by injection would yield a lower, and, we believe, less valid number for oral ingestion.

Under the Consent Decree in NRDC v. Train, criteria are to state "recommended maximum permissible concentrations (including where appropriate, zero) consistent with the protection of aquatic organisms, human health, and recreational activities." Beryllium is suspected of being a human carcinogen. Because there is no recognized safe concentration for a human carcinogen, the recommended concentration of beryllium in water for maximum protection of human health is zero.

Because attaining a zero concentration level may be infeasible in some cases and in order to assist the Agency and States in the possible future development of water quality regulations, the concentrations of beryllium corresponding to several incremental lifetime cancer risk levels have been estimated. A cancer risk level provides an estimate of the additional incidence of cancer that may be expected in an exposed population. A risk of 10^{-5} for example, indicates a probability of one additional case of cancer for every 100,000 people exposed, a risk of 10^{-6} indicates one additional case of cancer for every million people exposed, and so forth.

In the Federal Register notice of availability of draft ambient water quality criteria, EPA stated that it is considering setting criteria at an interim target risk level

of 10^{-5}, 10^{-6} or 10^{-7} as shown in the Table below.

Exposure Assumptions (per day)	Risk Levels and Corresponding Criteria (1)			
	0	10^{-7}	10^{-6}	10^{-5}
2 liters of drinking water and consumption of 18.7 grams fish and shellfish. (2)	0	0.00087 µg/l	0.0087 µg/l	0.087 µg/l
Consumption of fish and shellfish only.	0	.0056 µg/l	.056 µg/l	0.56 µg/l

(1) Calculated by applying a modified "one-hit" extrapolation model described in the Methodology Document to the animal bioassay data presented in Appendix I. Since the extrapolation model is linear at low doses, the additional lifetime risk is directly proportional to the water concentration. Therefore, water concentrations corresponding to other risk levels can be derived by multiplying or dividing one of the risk levels and corresponding water concentrations shown in the table by factors such as 10, 100, 1000, and so forth.

(2) 15 percent of the beryllium exposure results from the consumption of aquatic organisms which exhibit an average bioconcentration potential of 19 fold. The remaining 85 percent of beryllium exposure results from drinking water.

Concentration levels were derived assuming a lifetime exposure to various amounts of beryllium, (1) occurring from the consumption of both drinking water and aquatic life grown in waters containing the corresponding beryllium concentrations and, (2) occurring solely from consumption of aquatic life grown in the waters containing the corresponding beryllium concentrations. Because data indicating other sources of beryllium exposure and their contributions to total body burden are inadequate for quantitative use, the figures reflect the incremental risks associated with the indicated routes only.

Table 1. - Induction of osteosarcomas in experimental animals by beryllium

Compound	Dose	Exposure route	Exposure duration	Species	Percent responding[a]	Time of measurement (mos from start of treatment	References
Beryllium oxide	6 mg/m^3	Inhalation	5 hrs/day, 5 days/wk., 11 mos.	Rabbit	16	11	Dutra, et al. 1951
	Not reported	Multiple intravenous		Rabbit	25	Not reported	Nash, 1950
	90-660 mg as Be, 13-116 mg/kg body wt. as Be	17-21 intravenous injections		Rabbit	89	9+	Dutra & Largent, 1950
	100-200 mg total	1-45 intravenous injections		Rabbit	0	Not reported	Kawada, 1963
	1,250 mg total	Intravenous injection	25 wkly injections	Rabbit	72	Not reported	Fodor, 1971
	Large animals: 1 gm. total small animals: <1 gm.	Intravenous		Rabbit	6	15	Komitowski, 1969
	100 mg total	Injection into femur	10 wkly injections	Rabbit	60	19	Kawada, 1963
	450 mg total	Injection into femur	45 wkly injections	Rabbit	88	11	Kawada, 1963
	300 mg total	1 injection into femur		Rabbit	70	12	Kawada, 1963

[a]Percent exhibiting tumors or cancer.

Table 1. - (continued)

Compound	Dose	Exposure route	Exposure duration	Species	Percent responding	Time of measurement (mos)	References
Beryllium oxide	300 mg total	Injection, femur periosteum		Rabbit	78	14.5	Kawada, 1963
	10 mg	Implanted under right tibia periosteum		Rabbit male and female	33	10-25	Tapp, 1969
	220-400 mg	Injected into femur	Twice wkly for 1-43 weeks	Rabbit	89	85 days - average latency from last injection	Yamaguchi & Katsura, 1963
	420-600 mg	Injected into femur	Twice wkly for 1-43 weeks	Rabbit	100	85 days - average latency from last injection	Yamaguchi & Katsura, 1963
	620-800 mg	Injected into femur	Twice wkly for 1-43 weeks	Rabbit	50	85 days - average latency from last injection	Yamaguchi & Katsura, 1963
	820-860 mg	Injected into femur	Twice wkly for 1-43	Rabbit	75	85 days - average latency from last injection	Yamaguchi & Katsura, 1963
Zinc beryllium oxide	1 gm total	Intravenous	20 injections over 6 wks	Rabbit	100	7+	Gardner & Heslington, 1946
	1 gm	Multiple intravenous injections		Rabbit	25	30+	Barnes, et al. 1950 Simmons, 1950
	1 gm	Intravenous	22 semi-wkly injections	Rabbit	80	12+	Cloudman, et al. 1949

[a] 1 gram of zinc beryllium silicate contains 33.6 mg of Be expressed as the oxide

Table 1. - (continued)

Compound	Dose	Exposure route	Exposure duration	Species	Percent responding	Time of measurement (mos)	References
Zinc beryllium silicate	0.264 mg	Multiple intravenous injections		Mice	Some positive, percent not reported	Not reported	Cloudman, et al. 1949
	1 gm total	Intravenous	10 wkly injections	Rabbit	Some positive, percent not reported	11-24	Hoagland, et al. 1950
	1 gm total	Intravenous	20 twice-wkly injections	Rabbit	50	9-11	Janes, et al. 1954
	Not reported	Intravenous	10 wkly injections	Rabbit	71	9-14	Kelly, et al. 1961
	1 gm total	Injection	20 wkly injections	Rabbit	30	Not reported	Higgins, et al. 1964
	10 mg	Implanted under right tibia periosteum		Rabbit	16	10-25	Tapp, 1969
	33 mg as Be	Injection intra-osseous		Rabbit	70	4	Mazabraud, 1975
Beryllium silicate	10 mg	Implanted under right tibia periosteum		Rabbit	16	10-25	Tapp, 1969
Metallic beryllium	40 mg	Intravenous		Rabbit	40	Not reported	Barnes, et al. 1950

Table 1. - (continued)

Compound	Dose	Exposure route	Exposure duration	Species	Percent responding	Time of measurement (mos)	References
Beryllium phosphate	16 mg total	Injection	10 wkly injections	Rabbit	Some positive, percent unknown	11-24	Hoagland, et al. 1950
Beryllium phosphor[a]	90 mg	Intravenous		Rabbit	1/1	12-14	Dutra & Largent, 1950
	80 mg	Intravenous		Rabbit	1/1	12-14	Dutra & Largent, 1950
	64 mg	Intravenous		Rabbit	0/1	12-14	Dutra & Largent, 1950

[a]Be oxide, Zn oxide and silica in a molar ratio of 1:1:1

Table 2. - Induction of pulmonary cancer in experimental animals by beryllium

Compound	Dose	Exposure route	Exposure duration	Species	Percent responding	Time of measurement (mos)	References
Beryllium sulfate	.11 mg as Be	Intratracheal		Rat	Some positive, percent not reported	9 or longer	Vorwald & Reeves, 1959
	55 ug/m^3 as Be	Inhalation	6 hrs/day, 5 days/wk until sacrifice	Rat	Some positive, percent not reported	9 or longer	Vorwald & Reeves, 1959
	6 ug/m^3 as Be	Inhalation	6 hrs/day, 5 days/wk until sacrifice	Rat	Some positive, percent not reported	9 or longer	Vorwald & Reeves, 1959
	420 ug/m^3 35 ug/m^3 as Be	Inhalation	6 mos	Rat	Some positive, percent not reported	18	Schepers, 1961
	2.32 mg/m^3 0.20 mg/m^3 as Be	Inhalation	6 hr/day, 7 days	Monkey Macaca mullata	0, only 1 of 4 survived 180 days	6	Schepers, 1964
	42 ug/m^3 as Be	Inhalation	7 hrs/day, 5 days/wk, 18 mos.	Rat	Almost 100	18	Vorwald, et al. 1966
	21 ug/m^3 as Be	Inhalation	7 hrs/day, 5 days/wk, 18 mos.	Rat	Almost 100	18	Vorwald, et al. 1966
	2.8 ug/m^3 as Be	Inhalation	7 hrs/day, 5 days/wk. 18 mos.	Rat	62	18	Vorwald, et al. 1966
	35 ug/m^3 as Be	Inhalation	7 hrs/day, 5 days/wk, 18 mos.	Rhesus monkey	20, 2 of 10 exposed 3,241 & 3,871 hrs	5-6 yrs	Vorwald, et al. 1966
	34 ug/m^3 as Be	Inhalation	7 hrs/day, 5 days/wk, until sacrifice	Rat, male & female	100	13	Reeves, et al. 1967
Beryllium oxide	4.5 mg as Be	Intratracheal		Rat	Some positive, percent unknown	9 or longer	Vorwald & Reeves, 1959

Table 2. - (continued)

Compound	Dose	Exposure route	Exposure duration	Species	Percent responding	Time of measurement (mos)	References
Beryllium oxide	250-500 mg	Intratracheal and/or broncho-mural		Rhesus monkey	15	54+	Vorwald, et al. 1966
	25 mg calcined at 500°C	Intratracheal		Rat, males and females	100	15-20	Spencer, et al. 1968
	25 mg calcined at 1100°C	Intratracheal		Rat, males and females	25	15-17	Spencer, et al. 1968
	25 mg calcined at 1600°C	Intratracheal		Rat, males and females	30	18-24	Spencer, et al. 1968
	50 mg/kg calcined at 500°C	Intratracheal		Rat female	0	11	Spencer, et al. 1972
	50 mg/kg calcined at 500°C	Intratracheal		Rat, female	40	17	Spencer, et al. 1972
	50 mg/kg calcined at 500°C	Intratracheal		Rat, female	100	23	Spencer, et al. 1972
Beryllium fluoride	48 $\mu g/m^3$	Inhalation	6 mos	Rat	Some positive, percent unknown	15	Schepers, 1961
	950 $\mu g/m^3$ 180 $\mu g/m^3$ as Be	Inhalation	6 hrs/day, 7-16 days	Monkey Macacus mullata	0, all died within 28 days of exposure	less than 1	Schepers, 1964
Beryllium fluoride and chloride	0.2 or 0.4 mg/m^3	Inhalation	1 hr/day, 5 days/wk, 4 mos	Rat	Some positive, percent unknown	22	Litvinov, et al. 1975

Table 2. - (continued)

Compound	Dose	Exposure route	Exposure duration	Species	Percent responding	Time of measurement (mos)	References
Beryllium phosphate	3.5 mg/m^3	Inhalation	6 mos	Rat	Some positive, percent unknown	12	Schepers, 1961
	2.32 mg/m^3 0.20 mg/m^3 as Be	Inhalation	6 hrs/day, 30 days	Monkey *Macacus mullata*	0	up to 9 post-exposure	Schepers, 1964
	13.1 mg/m^3 1.11 mg/m^3 as Be	Inhalation	6 hrs/day, 10 days	Monkey *Macacus mullata*	25 of 4 exposed 1 survived 82 days post exposure and developed cancer	up to 82 days	Schepers, 1964
Zinc beryllium silicate	24 mg/m^3	Inhalation	6 mos	Rat	Some positive, percent unknown	9	Schepers, 1961
Beryl ore	15 mg/m^3 210 ug/m^3 as Be	Inhalation	6 hrs/day, 5 days/wk until sacrifice	Squirrel monkey *Salmiri sciurea*	0	23	Wagner, et al. 1969
	15 mg/m^3 210 ug/m^3 as Be	Inhalation	6 hrs/day, 5 days/wk until sacrifice	Rat	95	17	Wagner, et al. 1969
	15 mg/m^3 210 ug/m^3 as Be	Inhalation	6 hrs/day, 5 days wk until sacrifice	Hamster	0	17	Wagner, et al. 1969
Bertrandite ore	15 mg/m^3 620 ug/m^3 as Be	Inhalation	6 hrs/day, 5 days/wk until sacrifice	Squirrel monkey *Salmiri sciurea*	0	23	Wagner, et al. 1969

Table 2. - (continued)

Compound	Dose	Exposure route	Exposure duration	Species	Percent responding	Time of measurement (mos)	References
Bertrandite ore	15 mg/m^3 620 ug/m^3 as Be	Inhalation	6 hrs/day, 5 days/ wk until sacrifice	Rat	0	17	Wagner, et al. 1969
	15 mg/m^3 620 ug/m^3 as Be	Inhalation	6 hrs/day, 5 days/ wk until sacrifice	Hamster	0	17	Wagner, et al. 1969
Beryllium hydroxide	40 ug Be	Intratracheal		Rat 12 mo old	10	6	Groth & MacKay, 1971
	40 ug Be	Intratracheal		Rat 3 mo old	0	6	Groth & Mackay, 1971
	4 ug Be	Intratracheal		Rat 12 mo old	0	6	Groth, et al. 1972
	4 ug Be	Intratracheal		Rat 6 mo old	0	6	Groth,et al. 1972
	0.4 ug Be	Intratracheal		Rat 12 mo old	0	6	Groth, et al. 1976
	0.4 ug Be	Intratracheal		Rat 3 mo old	0	6	Groth, et al. 1976

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Appendix I

Derivation of Water Quality Criterion for Beryllium

Although beryllium was shown to produce bone osteosarcomas at an extremely low dose via intravenous injection (Cloudman, 1949), the experiments of Schroeder and Mitchener (1975) on rats and mice at 5 ppm in drinking water induced no observed carcinogenic response, except for a small statistically insignificant excess rate of "lymphoma leukemias" in female mice and in grossly observed tumors of all sites in male rats. The small absorption from the gastrointestinal tract is presumably the reason for the lack of significant effect. If beryllium is carcinogenic via ingestion it must be less potent than observed by Schroeder and Mitchener. Therefore, that experiment can be used to estimate the maximum risk that beryllium could pose, or equivalently, the lowest concentration which leads to a 10^{-5} lifetime risk.

In the male rats given 5 ppm in the drinking water, nine out of 33 treated animals had grossly observed tumors of some type, whereas four out of 26 controls had tumors. With a bioaccumulation factor of 1.0, the parameters of the extrapolation model are:

$n_t = 9$	le = 1126 days
$N_t = 33$	d = 5 ppm x 0.05 = 0.25 mg/kg/day
$n_c = 4$	L = 1126 days
$N_c = 26$	w = 0.385 kg
Le = 1126 days	R = 1.0

The result is that the water concentration does not need to get any lower than 0.10 micrograms per liter in order to keep the lifetime risk below 10^{-5}.